75. (Amended) The vector of claim 71, wherein said vector has substantially the same sequence as that shown in Figure 6 (SEQ ID NO: 5) and wherein said two copies of said encoded filamentous bacteriophage coat protein and said encoded fusion protein have the same function as that shown in Figure 2 (SEQ ID NO: 5).

REMARKS

Claims 1-5, 7, 16-32. 66-75 and 77 are pending in the above-identified application. Claims 1, 16, 26, 66, 70, 71 and 75 have been amended above. Support for the amendments can be found in the specification. Specifically, support for the amendment reciting that the functional heteromeric receptors are functional in the absence of its membrane attachment domain can be found, for example, on page 5, lines 14-23; page 5, lines 31-33; page 7, lines 10-13; page 11, lines 10-32; page 12, lines 5-8; page 12, line 29 through page 13, line 8, and throughout the Examples which describe the generation of functional heteromeric receptors that are functional in the absence of its membrane attachment domain. For example, support in the Examples can be found on page 34, lines 24-25; page 35, lines 18-19; page 37, line 35 through page 36, line 13, and page 40, lines 26-28. Support for the amendment reciting that the encoded coat and fusion proteins in the vector sequences of claims 70 and 75 have substantially the same sequence and the same function as the coat and fusion proteins encoded in SEQ ID NOS: 1 and 5 can be found, for example, on page 7, lines 10-13; page 8, lines 17-31, and in the Examples on, for example, pages 19-26. Accordingly, the

amendments do not introduce new matter and entry thereof is respectfully requested. A marked-up copy of the amended claims is attached hereto as Appendix A.

Formal figures 1 through 6, labelled in accordance with 37 C.F.R. § 1.84, are being submitted herewith to replace informal figures 1 through 6. Amendments have been made to the specification such that each reference to a figure corresponds with the appropriate formal drawing. These amendments do not add new matter, and Applicant respectfully requests entry of the amendments.

Applicant would like to thank Examiners Ulm and Eyler for extending a personal interview with Applicant and Applicant's representatives on December 17, 2002. As recorded in the Interview Summary, the rejections under 35 U.S.C. § 112, first and second paragraph were discussed. The amendments above and remarks below are believed by Applicant to substantially conform to the solutions discussed that would obviate the pending grounds of rejection.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-5, 7 and 77 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement because the specification does not adequately describe a method by which a heteromeric receptor is expressed on the surface of a cell.

Applicants maintain that the claims are sufficiently enabled because the application clearly sets forth teachings and guidance for expression of gene VIII fusion proteins on what Applicant regards as the surface of a cell and that which has been supported by extrinsic evidence of record. Nevertheless, Applicant has amended claim 1 above to remove reference to the location of the expressed gene VIII fusion protein because such description is unnecessary surplusage. Accordingly, this ground of rejection is rendered moot by the amendment and is respectfully requested to be withdrawn.

Claims 1-4, 7, 16-19, 21-29, 31, 32, 66-75, and 77 stand rejected under 35 U.S.C. §112, first paragraph, allegedly because the disclosure does not enable expression of functional portions, or sequences necessary for, any heteromeric receptor protein other than the variable heavy and variable light chains of immunoglobulins, on the surface of filamentous bacteriophage.

Applicant maintains that the claims as previously pending are sufficiently enabled to allow those skilled in the art to practice the invention as claimed. For the reasons of record, Applicant maintains that the claims do not encompass any heteromeric receptor, but instead, only those that maintain their ability to self-assemble into functional heteromeric receptors. Applicant has amended claims 1, 16, 26, 66 and 71 above to make clear that the claimed functional heteromeric receptors are functional in the absence of its membrane attachment domain. The application teaches, for example, at page 5, lines 14-23, that the heteromeric receptors of the invention consist of two or more

subunits which together exhibit binding activity towar4d a particular molecule and that it is understood by those skilled in the art that such heteromeric receptors include subunit fragments so long as assembly of the polypeptides and function is retained. Further, the amendment conforms to the discussions with Examiners Ulm and Eyler and noted in the Interview Summary of December 17, 2002. Accordingly, Applicant believes that the claims, as amended, are enabled and respectfully request that this ground of rejection be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 70 and 75 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite for reciting the phrase "has substantially the same sequence" in reference to the nucleotide sequences of the claimed vectors.

Applicant maintains for the reasons of record that the term is sufficiently clear to enable those skilled in the art to practice the invention as claimed. For example, in view of the teaching and guidance provided in the specification with regard to the pseudo-gene VIII and the wild-type gene VIII, as well as that which is well known to those skilled in the art, that those skilled would known what similarity between vectors would constitute a substantially similar sequence. Nevertheless, Applicant has amended claims 70 and 75 to recite that the claimed substantially similar sequence also exhibits the same function as the two copies of the filamentous bacteriophage coat protein and

the fusion protein encoded in the vector recited in Figure 2. As described above, Applicant has taught with reference to the gene VIII coat protein and fusion protein what constitutes substantially the same nucleotide sequences while still maintaining the same function of the encoded polypeptide. Accordingly, this ground of rejection is rendered moot by the amendment and is respectfully requested to be withdrawn.

Obvious-Type Double-Patenting Rejection

Claims 1-5, 7 and 16-33 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-32 of U.S. Patent Number 5,871,974. In making the rejection, the Office Action maintains that the pending claims are encompassed by the Patent claims and relies upon *Eli Lilly and Co. v. Barr Labs, Inc.* 222 F.3d 973, 55 USPQ2d 1609 (Fed. Cir. 2000) in alleging that in relation to an obviousness-type double patenting rejection, a species is obvious in view of the genus encompassing it.

Applicant maintain that pending claims 1-5, 7 and 16-33 are not obvious over claims 1-32 of U.S. Patent No. 5,871,974, because the plurality of cells recited in claims 1-5 and 7, are directed to the species "procaryotic cells" whereas the claims of the cited patent are directed to the genus "cells" and a genus does not, on its face, render obvious one of many particular species. As discussed at the personal interview, Applicant respectfully draws the Examiner's attention to the fact that the

the decision relied upon in the Office Action has been vacated by an *en banc* ruling of the Federal Circuit Court.

> Acting *en banc*, the court vacated the panel's original opinion entered on August 9, 2000, which is reported at 222 F.3d 973, 55 USPQ2d 1609 (Fed. Cir. 2000). The *en banc* court reassigned the opinion to the panel for a specific revision of the double patenting section. . . The panel's original judgement, which reversed the district court's determination that claim 7 of U.S. Patent No. 4,626,549 ("the '549 patent") is not invalid for double patenting, is reaffirmed, but on a different legal basis.

(emphasis added) *Eli Lilly and Co. v. Barr Labs, Inc.* 251 F3.d 955, 958, 58 USPQ2d 1865 (Fed. Cir. 2001). For the Examiner's convenience a copy of *Eli Lilly and Co. v. Barr Labs, Inc.* 251 F3.d 955 (Fed. Cir. 2001), is attached herewith as Exhibit A.

As set forth by the court, the legal basis upon which the *en banc* court decided invalidity for obviousness-type double patenting is non-analogous to the instant application. The legal basis upon which invalidity for double patenting was confirmed rested in part upon the conclusion that

> Our case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.

(emphasis added) 251 F3.d 955, 971. However, nowhere does the *en banc* court, in vacating its earlier decision, support an obviousness-type double patenting rejection of later species claims over earlier genus claims. Therefore, the final ruling of the court does not support the rejection of the pending claims, which recite the species "procaryotic cells," over the claims of the '974 patent, which recite the genus "cells." Accordingly, Applicant requests that rejection of claims 1-5, 7 and 16-33, under the judicially created doctrine of obviousness-type double patenting, be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect.

Should the Examiner have any questions, he/she is invited to call Cathryn Campbell or the undersigned agent.

Respectfully submitted,

January 13, 2003
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Serial No.: 08/471,622
Filed: June 5, 1995

APPENDIX A

In the specification:

On Page 4, please delete paragraphs 2 through 5 and substitute therefor:

[Figure 2]**Figures 2A, 2B and 2C** is the nucleotide sequence of M13IX30 (SEQ ID NO: 1).

[Figure 3]**Figures 3A, 3B and 3C** is the nucleotide sequence of M13IX11 (SEQ ID NO:2).

[Figure 4]**Figures 4A, 4B and 4C** is the nucleotide sequence of M13IX34 (SEQ ID NO: 3).

[Figure 5]**Figures 5A, 5B and 5C** is the nucleotide sequence of M13IX13 (SEQ ID NO: 4).

[Figure 6]**Figures 6A, 6B and 6C** is the nucleotide sequence of M13IX60 (SEQ ID NO: 5).

On page 7, please delete lines 1 through 17 and substitute therefor:

Expression of heteromeric receptors such as antibodies or functional fragments thereof on the surface of M13 can be

accomplished, for example, using the vector system shown in Figure 1. Construction of the vectors enabling one of ordinary skill to make them are explicitly set out in Example I. The complete nucleotide sequences are given in [Figures 2 and 3]**Figures 2A, 2B and 2C and Figures 3A, 3B and 3C** (SEQ ID NOS: 1 and 2). This system produces randomly combined populations of heavy (Hc) and light (Lc) chain antibody fragments functionally linked to expression elements. The Hc polypeptide is produced as a fusion protein with the M13 coat protein encoded by gene VIII. The gVIII-Hc fusion protein therefore anchors the assembled Hc and Lc polypeptides on the surface of M13. The diversity of Hc and Lc combinations obtained by this system can be 5×10^7 or greater. Diversity of less than 5×10^7 can also be obtained and will be determined by the need and type of heteromeric receptor to be expressed.

On page 26, please delete lines 16 through 31 and substitute therefor:

The third step in constructing M13IX30 involved inserting the expression and cloning sequences from M13IX04B upstream of the pseudo wild-type gVIII in M13IX01F. This was accomplished by digesting M13IX04B with Dra III and Bam HI and gel isolating the 700 base pair insert containing the sequences of interest. M13IX01F was likewise digested with Dra III and Bam HI. The insert was combined with the double digested vector at a molar ratio of 1:1 and ligated as described in Example I. The sequence of the final construct M13IX30, is shown in

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[Figure 2]**Figures 2A, 2B and 2C** (SEQ ID NO: 1). Figure 1A also shows M13IX30 where each of the elements necessary for surface expression of Hc fragments is marked. It should be noted during modification of the vectors, certain sequences differed from the published sequence of M13mp18. The new sequences are incorporated into the sequences recorded herein.

On page 29, please delete lines 17 through 21 and substitute therefor:

The sequence of the resultant vector, M13IX11, is shown in [Figure 3]**Figures 3A, 3B and 3C** (SEQ ID NO: 2). Figure 1B also shows M13IX11 where each of the elements necessary for producing a surface expression library between Lc fragments is marked.

On page 39, please delete line 10 through page 40, line 10 and substitute therefor:

M13IX34 (SEQ ID NO: 3) was created from M13IX33 by cloning in the gene encoding a human IgG1 heavy chain. The reading frame of the variable region was changed and a stop codon was introduced to ensure that a functional polypeptide would not be produced. The oligonucleotide used for the mutagenesis of the variable region was 5'-CACCGGTTCGGGGAATTAGTCTTGACCAGGCAGCCCAGGGC-3' (SEQ ID NO: 72). The complete nucleotide sequence of this

vector is shown in [Figure 4]**Figures 4A, 4B and 4C** (SEQ ID NO: 3).

Several vectors of the M13IX11 series were also generated to contain similar modifications as that described for the vectors M13IX53 and M13IX34. The promoter region in M13IX11 was mutated to conform to the 35 consensus sequence to generate M13IX12. The oligonucleotide used for this mutgenesis was 5'-ATTCCACACATTATACGAGCCCGGAAGCATAAAGTGCAAGCCTGGGGTGCC-3' (SEQ ID NO: 73). A human kappa light chain sequence was cloned into M13IX12 and the variable region subsequently deleted to generate M13IX13 (SEQ ID NO: 4). The complete nucleotide sequence of this vector is shown in [Figure 5]**Figures 5A, 5B and 5C** (SEQ ID NO: 4). A similar vector, designated M13IX14, was also generated in which the human lambda light chain was inserted into M13IX12 followed by deletion of the variable region. The oligonucleotides used for the variable region deletion of M13IX13 and M13IX14 were 5'-CTGCTCATCAGATGGCGGGAAGAGCTCGGCCATGGCTGGTTG-3' (SEQ ID NO: 74) and 5'-GAACAGAGT GACCGAGGGGGCGAGCTCGGCCATGGCTGGTTG-3' (SEQ ID NO: 75), respectively.

The Hc and Lc vectors or modified forms thereof can be combined using the methods described in Example I to produce a single vector similar to M13IX53 that allows the efficient incorporation of human Hc and Lc encoding sequences by mutagenesis. An example of such a vector is the combination of M13IX13 with M13IX34. The complete nucleotide sequence of this

vector, M13IX60, is shown in [Figure 6]**Figures 6A, 6B and 6C** (SEQ ID NO: 5).

In the claims:

1. (Amended) A composition of matter comprising a plurality of procaryotic cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form [functional] heteromeric receptors **functional in the absence of its membrane attachment domain**, said first and second DNA sequences contained in vectors, one or both of said polypeptides being expressed as a fusion protein with the protein product of gene VIII of a filamentous bacteriophage [on the surface of a procaryotic cell or a filamentous bacteriophage].

16. (Amended) A cloning system for the coexpression of two or more DNA sequences encoding polypeptides which form a heteromeric receptor **functional in the absence of its membrane attachment domain**, comprising a set of first vectors having a diverse population of first DNA sequences and a set of second vectors having a diverse population **of** second DNA sequences, said first and second vectors having two pairs of restriction sites symmetrically oriented about a cloning site for containing said first and second populations of DNA sequences, said two pairs of restriction sites in an opposite orientation with respect to the cloning site on each vector, sequences between said first pair of

restriction sites in said two vectors being homologous enough to allow annealing, and sequences between said second pair of restriction sites in said two vectors being homologous enough to allow annealing, so as to allow only the operational combination of vector sequences containing said first and second DNA sequences.

26. (Amended) A plurality of expression vectors, each vector containing a first and second DNA sequence encoding a first and second polypeptide of a heteromeric receptor, which form a plurality of heteromeric receptors **functional in the absence of its membrane attachment domain**, one or more of said receptors exhibiting binding activity toward a preselected molecule, said first or second DNA sequence being operatively linked to gene VIII of a filamentous bacteriophage.

66. (Amended) A vector comprising two copies of a gene encoding a filamentous bacteriophage coat protein, one copy of said gene being operationally linked to a DNA sequence encoding a polypeptide of a heteromeric receptor **functional in the absence of its membrane attachment domain**, said DNA sequence being expressed as a polypeptide of a fusion protein comprising said heteromeric receptor on the surface of said filamentous bacteriophage or as a soluble polypeptide.

70. (Amended) The vector of claim 66, wherein said vector has substantially the same sequence as that shown in Figure 2 (SEQ ID NO: 1) **and wherein said two copies of said**

encoded filamentous bacteriophage coat protein and said encoded fusion protein have the same function as that shown in Figure 2 (SEQ ID NO: 1).

71. (Amended) A vector comprising sequences necessary for the coexpression of two or more inserted DNA sequences encoding polypeptides which form heteromeric receptors **functional in the absence of its membrane attachment domain** and two copies of a gene encoding a filamentous bacteriophage coat protein, one copy of said gene being operationally linked to one of said two or more inserted DNA sequences, said DNA sequence being expressed as a polypeptide of a fusion protein comprising said heteromeric receptor on the surface of said filamentous bacteriophage or as a soluble polypeptide.

75. (Amended) The vector of claim 71, wherein said vector has substantially the same sequence as that shown in Figure 6 (SEQ ID NO: 5) **and wherein said two copies of said encoded filamentous bacteriophage coat protein and said encoded fusion protein have the same function as that shown in Figure 2 (SEQ ID NO: 5).**